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The sedation efficacy of different doses of remimazolam in elderly patients with regional nerve block anaesthesia

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Abstract

Background Remimazolam is a benzodiazepine sedative that is indicated for induction and maintenance during general anaesthesia. Remimazolam is also used for sedation in outpatient surgery; however, most reports have focused on nonelderly patients, whereas only a few studies have reported the use of remimazolam for elderly patients when receiving regional nerve block anaesthesia.

Aim The aim of this study was to evaluate the effects of different doses of remimazolam in elderly patients when specifically related to regional nerve block anaesthesia.

Methods This study was conducted at a university hospital between February 2022 and March 2023. We included 80 patients aged 65 years or older under regional nerve block anaesthesia. After the effects of anaesthesia were determined, patients were intravenously administered different doses of the test drug, i.e. 4, 4.5, 5, 5.5, or 6 mg, which were named the R1, R2, R3, R4, and R5 groups, respectively. The primary outcome was the loss of consciousness time. The secondary outcomes included the maintenance time and the number of assisted ventilators needed. The exceptional response of patients in terms of loss of consciousness maintenance time, the mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), SpO_2, and modified observers assessment of alertness/sedation (MOAA/S) scores were recorded at baseline (T0), 3 min after the injection of the test drug (T1), 6 min after the injection of the test drug (T2), 9 min after the injection of the test drug (T3), 12 min after the injection of the test drug (T4), 15 min after the injection of the test drug (T5), 18 min after the injection of the test drug (T6), 21 min after the injection of the test drug (T7), and 24 min after the injection of the test drug (T8).

Results We included 80 patients according to the inclusion and exclusion criteria, with 16 patients in each group. There were no significant differences in sex, age, and BMI amongst the 5 groups. The loss of consciousness time was significantly greater in the R2 group than in the R3, R4, and R5 groups ($p < 0.001$), and the loss of consciousness maintenance time was significantly greater in the R5 group than in the R3 group ($p < 0.05$). The MAP was significantly lower in the R2 and R5 groups than in the R1 group at T4 ($p = 0.004$) and significantly lower in the R5 group than in the R1 group at T5 ($p = 0.007$). The HR was significantly lower in the R5 group than in the R3 group at T3 ($p = 0.004$) and T4 ($p = 0.007$). The RR was significantly lower in the R5 group than in the R4 group at T4 ($p = 0.049$) and significantly greater in the R4 group than in the R2 group at T5 ($p = 0.024$) and T6 ($p = 0.020$). The RR was significantly lower

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in the R5 group than in the R1, R3 and R4 groups at T7 ($p=0.001$). The RR was significantly greater in the R1 group than in the R2 and R5 groups at T8 ($p=0.001$). The RR was significantly greater in the R4 group than in the R2 group at T8 ($p=0.001$). SpO_2 was significantly lower in the R3 group than in the R1 group at T3 ($p=0.003$) and significantly lower in the R3 group than in the R1 and R5 groups at T4 ($p=0.002$), T5 ($p=0.001$), T6 ($p=0.000$), and T7 ($p=0.000$). The MOAA/S scores were significantly lower in the R4 and R5 groups than in the R1 and R2 groups at T1 ($p=0.000$), significantly lower in the R5 group than in the R1 and R3 groups at T2 ($p=0.004$), and significantly lower in the R5 group than in the R1 group at T3 ($p=0.036$).

Conclusion The results indicated that doses of 5–5.5 mg remimazolam are more suitable for sedation in elderly patients, and the loss of consciousness time and depth of sedation differed according to the remimazolam dosage. Doses of 5–5.5 mg remimazolam were associated with adequate levels of sedation in elderly patients and with a decreased risk of complications, whilst haemodynamic fluctuations occurred approximately 12–15 min after the administration of remimazolam.

Keywords Remimazolam, Elderly patients, Dose, Regional nerve block

Introduction

Remimazolam was approved for the induction and maintenance of general anaesthesia in adults on January 23, 2020, in Japan [1, 2]. Remimazolam has an ester-linked side chain to the diazepine ring, making it an ultrashort-acting intravenous drug that is metabolized rapidly, mainly by liver tissue esterases. Remimazolam is a hepatic drug-metabolizing enzyme; however, since CYP is not involved in metabolism, its metabolites are not active [3, 4]. These characteristics suggest that remimazolam is safe and effective for a wide range of patients, including older adults and patients with unstable circulation. It is recommended that some fragile elderly patients receive lower doses of remimazolam anaesthesia [5, 6], but very few studies have focused on the optimal dose for senile patients. Hence, the aim of this study was to evaluate the optimal effective dose of remimazolam for senile patients receiving regional nerve block anaesthesia. We found that 5–5.5 mg remimazolam is more suitable for sedation in elderly patients and that a dose of 5–5.5 mg remimazolam was associated with an adequate level of sedation and a decreased risk of complications.

Materials and methods

Ethics approval was obtained from the ethics committee of The Second Affiliated Hospital of Xi'an Medical University (XZY202220), and the Helsinki Declaration was followed in the conduct of this research. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2400082092) and conducted according to the Consolidated Standards of Reporting Trials statement. Each participant provided written informed consent, and we provided participants with detailed information about the study aims, procedures, and risks before enrolling in the study.

Study design and patients

According to the sample calculation formula ($n=Z^2\alpha^2/e^2$), the minimum sample size is 68 cases. From February 2022 to March 2023, we controlled 80 patients who were older than 65 years and were under regional nerve block anaesthesia at the Department of Anaesthesiology, The Second Affiliated Hospital of Xi'an Medical University, Xi'an, China. The inclusion criteria were as follows: patients over 65 years of age who underwent elective surgery under regional nerve block anaesthesia, regardless of gender; American Society of Anaesthesiologists (ASA) grade II–III; and had a body mass index less than 30 kg/m^2. The patients or authorized family members provided written consent, were willing and able to comply with the research requirements, and agreed to a follow-up visit on the 7th day after surgery. The exclusion criteria included patients who: were allergic to benzodiazepine, nicotinamide, opioids or flumazenil; had a history of cerebral haemorrhage or cerebral infarction; had a history of long-term treatment with benzodiazepines for anxiety or insomnia; had a history of long-term use of opioids; had a history of regular use of illicit drugs, a history of drug abuse, or a positive drug screening test; had a history of alcohol or substance abuse in the past 2 years; had used of an investigational drug within 30 days prior to screening or within seven half-lives of the agent, whichever is longer; had participated in remimazolam clinical trials; and were unable to communicate and deemed not suitable for the study by the study's investigator.

Randomization and grouping

Patients were divided into 5 groups (16 patients in each group) via a random number table: the 4 mg remimazolam group (R1 group), the 4.5 mg remimazolam group (R2 group), the 5 mg remimazolam group (R3 group), the 5.5 mg remimazolam group (R4 group), and the 6 mg

remimazolam group (R5 group). First, the random number table method was used to ensure equal distribution amongst the five groups. Randomization was performed by opening a sealed envelope just before entry into the operating room by a nurse anaesthetist, who was not involved in the anaesthesia of the study participants. The nurse anaesthetist then prepared the medications, recorded the data according to the instructions inside the envelope, placed the recorded data back in the envelope and resealed the envelope. The anaesthesiologist administered intravenous drugs according to the instructions in the envelope. Finally, after the data of all the enrolled patients were collected, envelopes were opened by the investigators following good clinical practice (GCP). Thus, all patients, data collectors, and data analysts were blind to the group allocation.

Anaesthesia

Prior to surgery, a routine preoperative visit was conducted to ensure the patient's understanding and cooperation. Anaesthesia or epidural anaesthesia was used for all patients, and the effect of anaesthesia was tested to determine whether the brachial plexus block anaesthesia or the epidural anaesthesia was successful.

Remimazolam (Renfu Pharmaceutical Co. Ltd., approval number: 30T06081) was administered intravenously as follows: 4 mg for 60 s to Group R1 patients; 4.5 mg for 60 s to Group R2 patients; 5 mg for 60 s to Group R3 patients; 5.5 mg for 60 s to Group R4 patients; and 6 mg for 60 s to Group R5 patients.

Outcome measures

The primary outcomes were loss of consciousness time and loss of consciousness maintenance time. The secondary outcomes were haemodynamic parameters (HR, MAP), RR, SpO_2, MOAA/S, and adverse events. The exceptional responses of patients, including chewing (defined as the action of chewing food in the mouth), coughing (defined as a choking cough reaction), laboured respiration (defined as observing the patient experiencing respiratory distress or taking deep breaths following apnoea), limb movements (defined as involuntary movements of the upper or lower limbs), and hiccups (defined as sounds similar to "huh" emitted from the throat), were also recorded.

As soon as the patient entered the operating room, an electrocardiograph (ECG), noninvasive blood pressure, and pulse oximetry were routinely monitored, and peripheral venous access was established. Following at least 5 min of rest, the baseline data were recorded.

2.4.1 General data, including sex, age, height, weight, and body mass index (BMI), were recorded. The values of mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), SpO_2 and modified observers' assessment of alertness/sedation (MOAA/S) scores were recorded at baseline (5 min after arrival to the operating room) and then monitored and recorded at 3-min intervals during the observation period. The observation period included a loss of consciousness maintenance time. The loss of consciousness time (Loc from after the remimazolam injection until the eyelash-conditioned reflex disappeared) and the loss of consciousness maintenance time of the five groups of patients were recorded and compared. The loss of consciousness maintenance time (Locm) was defined as the time from losing consciousness to being fully awake (defined as 3 consecutive MOAA/S scores of 5). During the observation period, if oxygen saturation was < 90%, the patients were given pressure mask-assisted ventilation, and the number of required assisted ventilators was recorded. The exceptional response of patients during the loss of consciousness maintenance time was also recorded.

2.4.2 The occurrence of any adverse events was recorded. Adverse events were defined as any untoward medical occurrence during the hospital stay that was not necessarily need to be related to medication use. Adverse events were defined as an intraoperative systolic blood pressure exceeding ± 20% from the baseline value on two successive occasions or a heart rate greater than ± 20% above the baseline. If severe adverse events occurred, then the use of vasoactive drugs (atropine or ephedrine, noradrenaline or phenylephrine) and the name and dosage of the drug were recorded in detail.

Statistical analysis

SPSS 26.0 statistical software was used to test the normality of the data via the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared via analysis of variance (ANOVA) if the homogeneity of variance assumption was satisfied. Nonnormally distributed continuous variables and ordinal data were compared via the Kruskal–Wallis test, whilst categorical variables were compared with the $\chi 2$ test. Between-group comparisons were performed via one-way ANOVA, and $p < 0.05$ indicated that the difference was statistically significant.

After the statistical analysis, we found that our experimental data did not conform to a normal distribution. Therefore, we ultimately used the Kruskal–Wallis test for our experimental data.

Results

Baseline characteristics of the study participants

We included 80 patients according to the inclusion and exclusion criteria, with 16 patients in each group (Fig. 1).

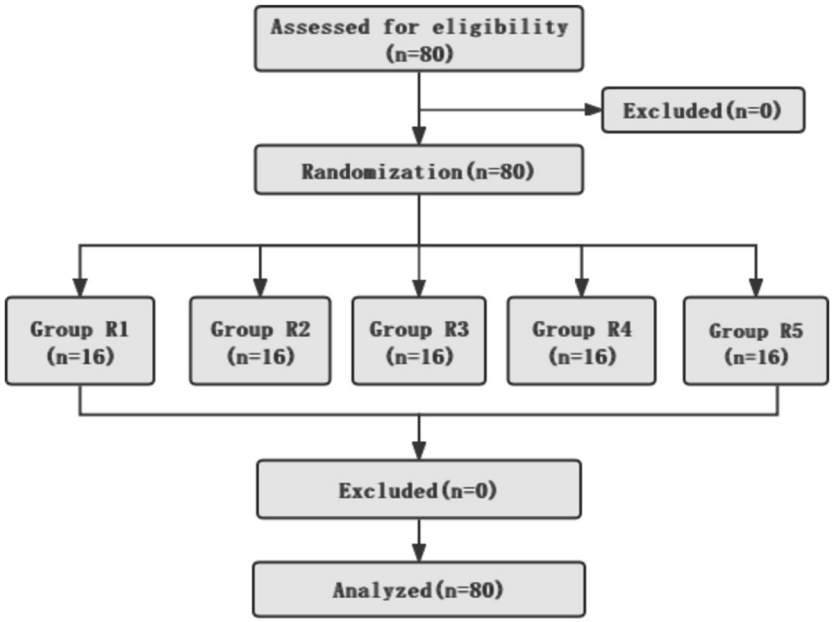

Fig. 1 Consort flow diagram of patients

Table 1 Baseline characteristics of the study participants

Group	Male/female (n)	Median age (years) (P25, P75)	Median (P25, P75) BMI (kg/m^2)
R1	7/9	70.00 (66.25, 73.75)	24.550 (22.075, 26.625)
R2	9/7	70.50 (67.25, 76.00)	22.250 (20.825, 24.750)
R3	12/4	74.00 (69.75, 82.5)	25.300 (22.600, 26.200)
R4	7/9	70.00 (68.00, 74.25)	24.950 (21.225, 26.325)
R5	8/8	72.00 (67.25, 74.50)	22.500 (21.625, 23.850)
H	–	7.188	8.479
p value	0.364	0.126	0.076

Data are presented as the median (P25, P75) ($n = 16$ in each group)

There were no significant differences in sex, age, or BMI amongst the 5 groups (Table 1).

Outcomes

Primary outcomes

The Loc and Locm values were recorded and compared (Table 2). Loc was significantly greater in the R2 group than in the R3, R4, and R5 groups ($p < 0.001$; Table 2). Locm was significantly greater in the R5 group than in the R3 group ($p < 0.05$; Table 2). There were no significant differences in Loc or Locm amongst the other groups (Table 2).

Table 2 Loc and Locm

Group	Median (P25, P75) Loc(s)	Median (P25, P75) Locm (s)
R1	62.00 (45.25, 113.00) ab	421.50 (352.00, 543.00) ab
R2	126.00 (78.00, 152.75) a	508.50 (508.50, 617.50) ab
R3	60.50 (45.00, 92.5) b	433.50 (291.75, 529.25) a
R4	51.00 (22.00, 71.50) b	499.00 (378.50, 862.50) ab
R5	55.50 (30.25, 117.00) b	667.00 (488.00, 776.25) b
H	20.947	10.689
p value	0.000	0.03

Data are presented as the median (P25, P75) ($n = 16$ in each group)

The same letter indicates no difference ($p > 0.05$) (a and a), and different letters indicate significant differences ($p < 0.05$) (a and b). *Loc* loss of consciousness time, *Locm* loss of consciousness maintenance time.

Secondary outcomes

The occurrence of any adverse events (including exceptional response and the use of vasoactive drugs) and the number of required cases of assisted ventilation (AV) were recorded (Table 3). The exceptional response of

Table 3 Exceptional response, vasoactive drugs, and AV

Group	Chew	Coughs	Laboured respiration	Limb movements	Hiccups	EP (mg)	AP (mg)	PE (ug)	AV
R1	2/16	4/16	0/16	0/16	0/16	0	0	0	0
R2	0/16	0/16	4/16	0/16	0/16	0	0	0	0
R3	0/16	1/16	0/16	4/16	0/16	0	1	80	2
R4	0/16	4/16	2/16	0/16	2/16	0	0	0	0
R5	1/16	6/16	6/16	0/16	0/16	20	0	0	4
Total	2/80	15/80	12/80	4/80	2/80	20	1	80	6

AP atropine, *EP* ephedrine, *PE* phenylephrine, *AV* assisted ventilation

patients during the loss of consciousness maintenance time was also recorded (Table 3). Exceptional responses included chewing, coughing, laboratory respiration, limb movements, and hiccups. In the R1 group, two patients (2/16) presented the same chewing response, and four patients (4/16) presented with a cough response. In the R2 group, four patients were observed for laboured respiration. In the R3 group, one patient experienced cough and four patients experienced limb movements for whom the total doses of atropine and phenylephrine were 1 mg and 80 μg, respectively, and two patients required assisted ventilation once. In the R4 group, four patients presented with cough, two patients presented with laboured respiration, and two patients presented with hiccups. In the R5 group, six patients experienced cough, six patients experienced laboured respiration for whom the total dose of ephedrine was 20 mg, and four patients required assisted ventilation once.

The values of the MAP, HR, RR, MOAA/S score and SpO_2 were recorded at baseline (T0), 3 min after the test drug injection (T1), 6 min after the test drug injection (T2), 9 min after the test drug injection (T3), 12 min after the test drug injection (T4), 15 min after the test drug injection (T5), 18 min after the test drug injection (T6), 21 min after the test drug injection (T7), and 24 min after the test drug injection (T8).

The MAP was significantly lower in the R2 and R5 groups than in the R1 group at T4 ($p=0.004$; Table 4) and significantly lower in the R5 group than in the R1 group at T5 ($p=0.007$; Table 4).

The HR was significantly lower in the R5 group than in the R3 group at T3 ($p=0.004$; Table 5) and T4 ($p=0.007$; Table 5).

The RR was significantly lower in the R5 group than in the R4 group at T4 ($p=0.049$; Table 6) and significantly greater in the R4 group than in the R2 group at T5 ($p=0.024$; Table 6) and T6 ($p=0.020$; Table 4). The RR

Table 4 Fluctuations in the mean arterial pressure (MAP) of the study participants (mmHg)

Group	T0	T1	T2	T3	T4
R1	91.5 (85.25,102.75)	91 (83.5,98)	91 (84.25,99.75)	92.5 (87.25,100)	98.5 (89.25,104.5)a
R2	88 (81.75,99.25)	82 (73.5,98.5)	82.5 (71,90.25)	82 (73.25,88.25)	84 (70,93)b
R3	90.5 (84.25,97.75)	85.5 (79.25,93.75)	84.5 (76,90.5)	83.5 (72.75,88.25)	85.5 (75.25,90)ab
R4	85.5 (79.25,106)	86.5 (72,98)	82.5 (69.75,94.5)	85.5 (71.5,94.25)	82.5 (72.25,95.75)ab
R5	94 (78.25,97.75)	84 (74,96.5)	81 (75,90)	82 (73,92.25)	79.5 (73.5,93.25)b
H	1.267	2.387	5.944	9.693	13.341
p value	0.737	0.496	0.114	0.021	0.004
Group	**T5**	**T6**	**T7**	**T8**	
R1	97 (87.25,105)a	93 (87.25,95)	93 (85.25,102)	92 (83.5,99.5)	
R2	86.5 (73,94)ab	85.5 (74.25,93)	88 (75,95.75)	86 (77.25,95.75)	
R3	85.5 (75.75,93.75)ab	84.5 (75.75,92.75)	89 (75.75,94)	88.5 (76.5,93)	
R4	84 (75.25,91)ab	83 (78,95.75)	85.5 (79.75,98)	84.5 (80,97)	
R5	80 (73.75,88)b	83.5 (77,93.5)	86.5 (78.25,94.25)	83 (76.5,94.5)	
H	12.075	5.716	3.902	3.253	
p value	0.007	0.126	0.272	0.354	

Data are presented as the median (P25, P75) ($n=16$ in each group). The same letter indicates no difference ($p>0.05$) (a and a), and different letters indicate significant differences ($p<0.05$) (a and b).

Table 5 Fluctuations in the heart rate (HR) of the study participants (beats/minute)

Group	T0	T1	T2	T3	T4
R1	66 (57.25,69.75)	72 (56.25,80.75)	69 (55.5,74.75)	66.5 (55.25,77.5)ab	67 (60,74.75)ab
R2	73.5 (62.5,84)	79.5 (66.5,82)	77 (62.5,82.5)	70.5 (61.75,77.5)ab	71.5 (61,77)ab
R3	67 (62.5,77)	75 (68.5,90.75)	70.5 (64.25,91.25)	72 (63.25,86)a	71 (64.75,78.25)a
R4	66 (57.5,71.75)	70 (58.5,75.75)	66.5 (63.5,70)	65.5 (57,67.75)ab	66.5 (59.75,70.25)ab
R5	64 (55.25,71.75	69 (61,76.25)	67 (59,72.5)	62.5 (54.75,69.25)b	61.5 (52.25,69.25)b
H	2.796	6.780	4.423	7.262	5.186
p value	0.424	0.079	0.219	0.044	0.024
Group	**T5**	**T6**	**T7**	**T8**	
R1	66 (59,72.75)	65.5 (56.5,75)	65 (57,78)	66.5 (57.5,78.75)	
R2	71.5 (59.25,74.75)	66.5 (62.25,74.25)	68.5 (63,77)	70.5 (65,79.5)	
R3	67 (62,77.5)	69.5 (64.25,76.5)	69.5 (63.5,77.5)	69 (62.25,77.25)	
R4	69 (56.25,71.5)	67.5 (59.75,72.5)	68 (63.25,71)	67 (62.25,71.75)	
R5	62 (53.5,70.25)	60 (56.25,71.25)	60.5 (57.25,71)	61 (56.75,69.5)	
H	1.477	2.668	1.955	3.069	
p value	0.688	0.446	0.582	0.381	

Data are presented as the median (P25, P75) ($n=16$ in each group). The same letter indicates no difference ($p>0.05$) (a and a), and different letters indicate significant differences ($p<0.05$) (a and b).

Table 6 Fluctuations in the respiratory rate (RR) of the study participants (beats/minute)

Group	T0	T1	T2	T3	T4
R1	18 (18,20)a	18 (15.75,20)	17.5 (13.75,18)	18 (18,18)	18 (18,19.5)ab
R2	18 (18,19.5)ab	17 (16,18)	18 (16.25,20)	17.5 (16,18)	18 (16.5,18)ab
R3	19 (18,20)a	18 (17,20)	18 (17,20)	18 (18,19.75)	18 (17,19.5)ab
R4	19 (16.5,20)a	19 (18,25)	19 (18,20)	18 (18,19.75)	18 (18,20)a
R5	16 (14.25,18)b	18 (18,20)	17.5 (14.5,18.75)	17 (15.25,19.5)	16 (14.5,18)b
H	17.376	6.494	9.136	4.402	9.554
p value	0.002	0.165	0.058	0.354	0.049
Group	**T5**	**T6**	**T7**	**T8**	
R1	18 (18,20)ab	18 (17.25,20)ab	18 (18,20)a	18 (18,20)a	
R2	17 (16.25,18)a	16 (16,18)a	17 (16,18)ab	16.5 (16,18)b	
R3	18 (18,19,5)ab	18 (17,19.5)ab	18 (18,19.5)a	18 (16.25,19.5)ab	
R4	19 (178,20)b	18 (18,20)b	18 (18,19.5)a	19 (18,20)a	
R5	18 (15.25,19.5)ab	16.5 (16,18)ab	16 (15,17.75)b	15.5 (14.25,18)b	
H	11.266	11.722	18.093	18.771	
p value	0.024	0.020	0.001	0.001	

Data are presented as the median (P25, P75) ($n=16$ in each group). The same letter indicates no difference ($p>0.05$) (a and a), and different letters indicate significant differences ($p<0.05$) (a and b).

was significantly lower in the R5 group than in the R1, R3, and R4 groups at T7 ($p=0.001$; Table 6). The RR was significantly greater in the R1 group than in the R2 and R5 groups at T8 ($p=0.001$; Table 6). The RR was significantly greater in the R4 group than in the R2 group at T8 ($p=0.001$; Table 6).

SpO_2 was significantly lower in the R3 group than in the R1 group at T3 ($p=0.003$; Table 7) and significantly lower in the R3 group than in the R1 and R5 groups at T4 ($p=0.002$; Table 7), T5 ($p=0.001$; Table 7), T6 ($p=0.000$; Table 7), and T7 ($p=0.000$; Table 7).

The MOAA/S scores were significantly lower in the R4 and R5 groups than in the R1 and R2 groups at T1 ($p=0.000$; Table 8), significantly lower in the R5 group than in the R1 and R3 groups at T2 ($p=0.004$; Table 8), and significantly lower in the R5 group than in the R1 group at T3 ($p=0.036$; Table 8).

Table 7 Fluctuations in the SpO_2 of the study participants (%)

Group	T0	T1	T2	T3	T4
R1	100 (99.25,100)ab	100 (97,100)	100 (100,100)	100 (99.25,100)a	100 (100,100)a
R2	99.5 (99,100)ab	99.5 (98.25,100)	99.5 (99,100)	99.5 (99,100)ab	100 (99,100)ab
R3	99 (99,100)a	97 (94,100)	98.5 (97.25,99.75)	98.5 (97,99.75)b	98.5 (98,100)b
R4	100 (98,100)ab	99 (97.25,100)	100 (98.5,100)	100 (99.25,100)ab	100 (99.25,100)ab
R5	100 (100,100)b	97.5 (88.25,100)	99 (99,100)	100 (99.25,100)ab	100 (100,100)a
H	15.262	7.896	7.212	15.772	16.739
p value	0.004	0.095	0.125	0.003	0.002

Group	T5	T6	T7	T8
R1	100 (100,100)a	100 (100,100)a	100 (100,100)a	100 (99.25,100)
R2	100 (99,100)ab	100 (99,100)ab	100 (99,100)ab	100 (99.25,100)
R3	98.5 (98,100)b	98.5 (98,100)b	98.5 (97.25,100)b	99 (98,100)
R4	100 (99.25,100)ab	100 (99.25,100)ab	100 (99.25,100)ab	100 (99.25,100)
R5	100 (100,100)a	100 (100,100)a	100 (100,100)a	100 (100,100)
H	18.394	20.081	20.495	9.050
p value	0.001	0.000	0.000	0.060

Data are presented as the median (P25, P75) ($n = 16$ in each group). The same letter indicates no difference ($p > 0.05$) (a and a), and different letters indicate significant differences ($p < 0.05$) (a and b).

Table 8 Fluctuations in MOAA/S of the study participants (scores)

Group	T0	T1	T2	T3	T4	T5	T6	T7	T8
R1	5 (5,5)	2.5 (1,4)a	4 (2,4)a	5 (4,5)a	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)
R2	5 (5,5)	2.5 (1,3.75)a	2.5 (1.25,4.5)ab	3.5 (2.25,5)ab	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)
R3	5 (5,5)	1 (0,1.75)ab	3 (1.25,4.75)a	5 (2.5,5)ab	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)	5 (5,5)
R4	5 (5,5)	0 (0,1)b	1 (0.25,3.75)ab	4.5 (4,5)ab	5 (4,5)	5 (4.25,5)	5 (5,5)	5 (5,5)	5 (5,5)
R5	5 (5,5)	0 (0,0.75)b	0.5 (0,1.75)b	3 (0.25,4.75)b	5 (1.5,5)	5 (4.25,5)	5 (5,5)	5 (5,5)	5 (5,5)
H	0.000	27.325	15.575	10.270	7.315	5.972	8.272	8.103	8.103
p value	1.000	0.000	0.004	0.036	0.120	0.201	0.082	0.088	0.088

Data are presented as the median (P25, P75) ($n = 16$ in each group). The same letter indicates no difference ($p > 0.05$) (a and a), and different letters indicate significant differences ($p < 0.05$) (a and b).

Discussion

Elderly patients, as a special group, have low body resistance and are often confronted with with multiple underlying diseases, thus resulting in high requirements for perioperative anaesthesia [7, 8]. Studies have shown that the drug concentration in elderly patients is significantly increased, resulting in enhanced drug effects; thus, the respiratory and circulatory inhibitory effects of anaesthetics in elderly patients are significantly stronger than those in young patients, and the drug elimination half-life is longer in elderly patients [9]. This causes large fluctuations in the circulatory system during surgical anaesthesia. As a novel benzodiazepine drug characterized by ultrashort sedative and hypnotic effects, remimazolam has been introduced into clinical practice for sedation and general anaesthesia with no reported severe adverse events associated with remimazolam sedation [10]. However, very few studies have focused on the optimal dose for elderly patients. The current clinical recommendation for the initial dose of remimazolam is 0.15 to 0.20 mg/kg. Studies have shown that, owing to the linear pharmacokinetic characteristics of remimazolam, there is no significant difference between administering a fixed dose and a dose based on the body weight for patients weighing 60–100 kg [11]. Therefore, a fixed-dose administration method was selected for this trial.

In endoscopic sedation and other clinical trials, the incidence of respiratory depression in the remimazolam groups ranged from 1.1 to 4% [12–14]. These subjects were all nonelderly patients. In our study, we found that there were no severe adverse events associated with remimazolam sedation; however, in the 6 mg remimazolam group, 4 patients needed assisted ventilation, and in the 5.5 mg remimazolam group, no patients needed vasoactive drugs. In the 6 mg remimazolam group, 6 patients experienced laboured respiration, and in the 5 mg

remimazolam group, no patients experienced laboured respiration. After respiratory depression occurs, it can usually be alleviated within a short period of time following conventional management measures (such as the jaw thrust manoeuvre) [15]. This was confirmed in our study. For these reasons, we believe that 5–5.5 mg remimazolam is more suitable for elderly patient sedation. Studies have shown that remimazolam takes effect approximately 1–3 min after a single dose, with a duration of action that fades away within 6.8–9.9 min [16]. In one study, the median recovery time from the discontinuation of remimazolam to extubation was approximately 7 min without flumazenil [17], but the research subjects were not elderly patients. In our study, the minimum loss of consciousness time was 51 s in the 5.5 mg remimazolam group, and the minimum loss of consciousness maintenance time was 421 s in the 4 mg remimazolam group. For these reasons, we believe that the remimazolam dosage should be reduced for elderly patients. We also found that the loss of consciousness time differed amongst the different remimazolam dosages. Furthermore, we detected several exceptional responses, including chewing, coughing, laboured respiration, limb movements, and hiccups. These responses have not been addressed in previous studies.

The haemodynamic profile of patients treated with remimazolam is stable [1]. In a comparative analysis involving remimazolam and propofol, patients who were administered remimazolam experienced a notably reduced occurrence of intraoperative hypotension [18]. In phase II and III clinical trials for sedation or anaesthesia during endoscopic procedures, the incidence of blood pressure decrease in the remimazolam groups ranged from 0 to 30% [12–14, 19–21]. In our study, the MAP was significantly lower in the 4.5 mg and 6 mg remimazolam groups than in the 4 mg remimazolam group at 12 min following the remimazolam injection and significantly lower in the 6 mg remimazolam group than in the 4 mg remimazolam group at 15 min after the remimazolam injection. In our study, the HR was significantly lower in the 6 mg remimazolam group than in the 5 mg remimazolam group at 12 min and 15 min after injection. For these reasons, we believe that haemodynamic fluctuations occurred approximately 12–15 min after the administration of remimazolam for elderly patient sedation. In our study, the respiratory rate was lower in the 6 mg remimazolam group than in the other groups but was still within normal range. However, in the 6 mg remimazolam group, four patients required assisted ventilation once. Thus, the respiratory system should be closely monitored after the administration of 6 mg or more of remimazolam for elderly patient sedation. In our study, the SpO_2 was lower in the 5 mg remimazolam group than in the other groups, but it was still within normal range. Our study revealed that satisfactory sedation was obtained in 100% of patients based on MOAA/S, although the depth of sedation differed amongst the different remimazolam dosages.

Our study had several limitations. First, our study has a relatively small sample size. Second, the age categorization of the patients in our study was not sufficiently detailed. Future research should separate the very elderly patients for a more thorough investigation. Third, in clinical trials, whilst the use of a dose-escalation design can better identify the maximum tolerated dose and optimal therapeutic effect, our study did not employ this method.

Conclusion

In conclusion, we believe that 5–5.5 mg remimazolam is more suitable for sedation in elderly patients. The remimazolam dosage should be reduced for sedation in elderly patients. Both the loss of consciousness time and the depth of sedation vary based on the different remimazolam dosages. Haemodynamic fluctuations occur approximately 12–15 min after the administration of remimazolam for sedation in elderly patients. Furthermore, respiratory factors should be closely monitored after the administration of remimazolam for sedation in elderly patients. Overall, it was determined that a dose of 5–5.5 mg remimazolam is associated with an adequate level of sedation with a decreased risk of complications, although several exceptional responses, including chewing, coughing, laboured respiration, limb movements, and hiccups, were observed.

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All authors have made substantial contributions to this work. We have jointly conducted research, analyzed data, and developed the ideas presented in the article. Each author has also participated in the writing and revision process, ensuring the accuracy, coherence, and originality of the final manuscript.

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Data availability

No datasets were generated or analyzed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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